Alerts, Notices, and Case Reports

Paralytic Shellfish Poisoning in Kodiak, Alaska

BRADFORD D. GESSNER, MD
JOHN P. MIDDAUGH, MD
Anchorage, Alaska
GREGORY J. DOUCETTE, PhD
Charleston, South Carolina

PARALYTIC SHELLFISH POISONING (PSP) occurs worldwide and its incidence may be increasing.[1] In North America PSP has been reported mainly in Canada, the Pacific Northwest, California, and New England. Paralytic shellfish poisoning is caused by ingestion of shellfish containing one or more of several saxitoxin analogs.[2] Saxitoxins act by blocking sodium ion movement through voltage-gated sodium channels on excitable cell membranes.[2] Generally, PSP results in mild symptoms such as paresthesias, including perioral and extremity numbness and tingling, and gastrointestinal symptoms, including nausea and vomiting.[3,4] More severe cases may result in neurologic symptoms such as dysarthria, dysphagia, ataxia, diplopia, weakness, and a dissociative feeling. Death is unusual and generally results from respiratory paralysis. In severe cases, progression from onset of symptoms to respiratory arrest may be rapid. The case reported here occurred as part of a larger outbreak that has recently been described in full.[5]

Report of a Case

This 28-year-old man presented to the hospital on May 24, 1994, with gastrointestinal and neurologic symptoms.

The patient had been in good health until 4 hours previously when he experienced the acute onset of perioral paresthesias, nausea, and vomiting. He subsequently suffered progressive severe headache, dysarthria, dysphagia, and ataxia and presented to a local hospital. During triage evaluation, the patient was anxious and had pink skin and mucous membranes. His blood pressure was 172/110 mmHg, his pulse 83, and his oxygen saturation 97%. Fifteen minutes later he became apneic and cyanotic while his oxygen saturation decreased sharply to 55%. After a brief period of bag and mask ventilation, he was intubated with an endotracheal tube and mechanically ventilated.

The patient was a recent immigrant from El Salvador who spoke little English and worked for a fish cannery. He had a past history of gastric bleeding 2 years previously but was taking no medications at the time of his current illness. One to two hours before illness onset, he had been drinking beer and collecting, roasting, and eating mussels from a beach on Kodiak Island. He had no recent history of trauma, fever, or upper respiratory symptoms.

On rapid physical examination following the onset of apnea, the patient was afebrile with a blood pressure of 244/131 mmHg and a pulse of 135. His head, neck, lymph nodes, lungs, heart, abdomen, and skin were normal. On neurologic examination, his pupils were sluggishly reactive and dilated and he was areflexic and unresponsive to vocal or pain stimuli.

The patient's complete blood count and serum levels of electrolytes, glucose, calcium, blood urea nitrogen, creatinine, and creatine kinase were normal; his serum lactic acid dehydrogenase was 196 U per liter (normal range 0–190 U/L). Toxicology screening was negative except for an ethyl alcohol level of 10 mg/dL. Testing for arterial blood gas levels performed after respiratory arrest and during bag and mask ventilation with 100% oxygen yielded a pH of 7.3, PaO_2 of 196 mmHg, a $PaCO_2$ of 28 mmHg, and a bicarbonate of 14 mEq/L. On chest radiographic examination he displayed left lower lobe atelectasis and an electrocardiograph demonstrated sinus tachycardia. Computerized tomography scans of the abdomen, chest, and head were unrevealing. Treatment consisted of supportive care and management of hypertension.

During neurologic examination 4 hours after respiratory arrest, the patient did not respond to voice commands, his pupils were fixed and dilated, his fundoscopic examination was normal with clear disc margins, he displayed no facial grimace when a cotton swab was applied to his nasopharynx, showed no response to finger nail compression, his doll's eyes maneuver test was negative, and Babinski, cremasteric, abdominal, and deep tendon reflexes were absent. At this point the patient was not receiving sedative or paralytic medications. Consideration was given to performing tests to determine the possibility of brain death until a diagnosis of paralytic shellfish poisoning was taken into account.

Five hours after intubation, the patient moved his toes spontaneously; 30 minutes later he opened his eyes and breathed against the ventilator. He subsequently extubated himself and was reintubated after receiving vecuronium bromide and diazepam. Fifteen hours after his respiratory arrest, following a period of increasing

(Gessner BD, Middaugh JP, Doucette GJ. Paralytic shellfish poisoning in Kodiak, Alaska. West J Med 1997 Nov; 166:351–353)

From the Alaska Division of Public Health, Anchorage; and the United States Department of Commerce, National Oceanic and Atmospheric Administration, National Marine Fisheries Service, Southeast Fisheries Science Center, Charleston, South Carolina.

Reprint requests to Bradford D. Gessner, MD, Alaska Division of Public Health, 1231 Gambell St, 2nd Floor, Anchorage, AK 99501.

consciousness during which he continued to receive diazepam intermittently, his endotracheal tube was removed. Thirty-two hours after respiratory arrest, the patient was awake, oriented to person, place, and time, and complained only of weakness, although he could walk without assistance. He had no dysphagia, dysarthria, or diplopia. On examination, he had a diminished but present gag reflex, normal deep tendon and absent Babinski reflexes, and normal cranial nerve (II–XII) function.

The course of the patient's hypertension reached a peak 6 to 7 hours after presentation or 11 to 12 hours after eating mussels. This hypertension was refractory to two 1-mg intravenously administered doses of metaprolol and a 10-mg dose of nifedipine administered sublingually approximately 5 hours after presentation and a 10-mg dose of nifedipine administered 6 hours after presentation. Between 7 and 8 hours after presentation, and 2 to 3 hours after the gradual return of neurologic function, the patient's blood pressure began to decrease; 24 hours after presentation it measured 108/61 mmHg.

Subsequent testing of mussels from the implicated beach detected a PSP toxin concentration of 18,684 μg per 100 g of tissue; based on a body weight of 91 kg, the patient ate an estimated 411 μg toxin per kg body weight. An analysis of the PSP toxin components showed that the most prevalent compounds were gonyautoxin 2 (22.8 mole percent), gonyautoxin 1 (19.5 mole percent), C1 (16.1 mole percent), gonyautoxin 3 (14.2 mole percent), and C2 (12.0 mole percent).

Discussion

This case illustrates the dramatic onset, presentation, and recovery commonly associated with severe PSP and emphasizes how important it is that health care providers recognize the symptoms of this disease. The initial clinical presentation of PSP may resemble that associated with ingestion of other toxins found in seafood, including tetrodotoxin and ciguatoxin,[6,7] as well as poisoning by pesticides containing anticholinesterases.[8] In areas such as Alaska, botulism must also be included in the differential diagnosis. Severe PSP may present with, or rapidly progress to, respiratory arrest[3,4] and (as was seen in the case we present) a clinical picture resembling deep coma. Unless clinicians consider the possibility of PSP, an unnecessarily extensive diagnostic workup may be undertaken. More tragically, in areas where sophisticated mechanisms to determine brain death do not exist, health care providers may decide that further therapeutic intervention is futile and discontinue life support measures. Fortunately, the physicians caring for the patient presented here recognized that his symptoms might be consistent with PSP, despite a clinical picture that resembled deep coma.

Using an animal model, Benton et al demonstrated the reversal of cardiorespiratory arrest using an α-saxitoxin antibody;[9] other studies have suggested that ethyl alcohol ingestion may protect against the effects of PSP toxins.[4,10] Despite these findings, the clinical management of patients with PSP remains largely life supportive. Charcoal and gastric lavage may be attempted[8] regardless of a history of having vomited, because in at least one other report the authors describe a patient who had significant amounts of shellfish in her stomach at autopsy despite vomiting before death.[8] Respiratory support should be provided until the return of adequate respiratory function. When initiated before hypoxic damage, ventilator support may lead to rapid and complete recovery.[3,4] Clinicians should be aware that, although cardiac sodium channels are relatively resistant to saxitoxins, PSP toxins may act directly on cardiac tissue and at high concentrations may lead to significant cardiac effects, including cardiovascular failure.[5,11–13]

Few investigators have attempted to evaluate the effect of paralytic shellfish poison toxin on blood pressure, although one investigation in which blood pressure measurements were documented found hypertension.[10] Similarly, the patient described in the current report had evidence of systemic arterial hypertension at the time of presentation. Despite pharmacological intervention and his unconscious state, his hypertension did not resolve until after the return of neurologic function. The mechanism of PSP toxin–induced hypertension is not known, and therefore specific treatment recommendations cannot be made. The lack of response to nifedipine and metaprolol in our patient suggests that his hypertension was not the result of changes in calcium channel or β-adrenergic activity.

Most previous investigations of PSP outbreaks have not attempted to define the minimum lethal concentration of the toxin per body weight. One team of investigators has identified saxitoxin B1 as the principal toxin and estimated the lethal concentration to be 86 to 788 μg per kilogram of body weight.[3] We have found that with predominant shellfish toxin components of C1, C2, and the gonyautoxins, 411 μg per kilogram of body weight constitutes a lethal concentration in the absence of respiratory support.

Because recovery with respiratory support may be rapid and complete, health care providers should know the signs, symptoms, and appropriate management of PSP. In addition, they should report all suspected cases of PSP to local health authorities so that appropriate warnings may be issued and further cases prevented.

REFERENCES

1. Anderson DM. Red tides. Scientif Am 1994; 271:62–68

2. Hall S, Strichartz G, Moczydlowski E, Ravindran Q Reichardt PB: The saxitoxins: sources, chemistry, and pharmacology. *In:* Hall S, Strichartz GR (Eds.): Marine toxins: origin, structure, and molecularpharmacology. American Chemical Society Symposium Series No 418. Washington, DC: American Chemical Society, 1990; pp 29–65

3. Rodrigue BC, Etzel RA, Hall S, et al. Lethal paralytic shellfish poisoning in Guatemala. Am J Trop Med Hyg 1990;42:267–271

4. Gessner BD, Middaugh JP. Paralytic shellfish poisoning in Alaska: a 20-year retrospective analysis. Am J Epidemiol 1995; 141:766–770

5. Gessner BD, Bell P, Doucette GJ, Moczydlowski E, Poll Mg Van Dolah F, et al. Hypertension and identification oftoxin in human urine and serum following a cluster of mussel-associated paralytic shellfish poisoning outbreaks. Toxicon (In press)

6. Sakamoto Y, Lockey RF, Krzanowski JJ. Shellfish and fish poisoning related to the toxic dinoflagellates. South Med J 1987; 80:866–872

7. Eastaugh J, Shephard S. Infectious and toxic syndromes from fish and shellfish consumption. Arch Intern Med 1989; 149:1735–1740

8. Kao CY. Paralytic shellfish poisoning. *In*: Falconer IR (Ed.): Algal toxins in seafood and drinking water. Orlando: Academic Press, 1993; pp 75–86

9. Benton BJ, Rivera VR Heweston JF, et al. Reversal ofsaxitoxin-induced cardiorespiratory failure by a burro-raised α-saxitoxin-antibody and oxygen therapy. Toxicol Appl Pharmacol 1994; 124:39–51

10. McCollum JFK, Pearson RCM, Ingham HR, Wood PC, Dewar HA. An epidemic of mussel poisoning in North-East England. Lancet 1968; 2:767–770

11. Chang FT, Benton BJ, Lent Rq et al. Central and peripheral cardio-respiratory effects of saxitoxin (STX) in urethane-anesthetized guinea-pigs. Toxicon 1993; 31:645–664

12. Doyle DD, Guo Y, Lustig SL, et al. Divalent cation competition with [^{3}H]saxitoxin binding to tetrodotoxin-resistant and -sensitive sodium channels: a two-site structural model ofion/toxin interaction. J Gen Physiol 1993; 101:153–182

13. Heinemann SH, Terlau H, Imoto K: Molecular basis for pharmacological differences between brain and cardiac sodium channels. Pflugers Arch 1992; 422:90–92

Resolution of Propylthiouracil-Induced Hepatic Failure After Treatment of Thyrotoxicosis

WEERAPAN KHOVIDHUNKIT, MD
ROBERT V. FARESE, JR., MD
San Francisco, California

A RELATIONSHIP between thyroid diseases and the liver has been recognized for more than a century.[1] Hepatic dysfunction has been found in cases of long-standing hyperthyroidism, usually in association with congestive heart failure.[2,3] Elevated levels of serum transaminase, alkaline phosphatase (ALP), and bilirubin are frequently observed in thyroid storm. In rare cases, patients suffering from hyperthyroidism presented with signs and symptoms of liver disease, which disappeared after successful treatment of thyrotoxicosis.[4–8] With the introduction of effective treatments for hyperthyroidism, jaundice and hepatic dysfunction are now uncommon in patients with hyperthyroidism; however, hepatotoxicity from propylthiouracil (PTU) or methimazole remains a rare but well-established complication in these patients.[9] In most cases, liver function improves after antithyroid drugs are discontinued, although fatal cases of PTU-induced hepatic failure have been reported.[10–13] In the present report we describe a case of Graves' disease complicated by PTU-induced hepatic necrosis associated with persistent severe thyrotoxicosis. Hepatic failure resolved after treatment of thyrotoxicosis, suggesting that achievement of a euthyroid state may be of great benefit in such cases.

(Khovidhunkit W, Farese RV Jr. Resolution of propylthiouracil-induced hepatic failure after treatment of thyrotoxicosis. West J Med 1997 Nov; 166:353–356)

From the Division of Endocrinology and Metabolism, Department of Medicine (Drs Khovidhunkit and Farese) and the Gladstone Institute of Cardiovascular Disease (Dr Farese), University of California, San Francisco, California.

Reprint requests to Weerapan Khovidhunkit, MD, Medical Service, Division of Endocrinology (111N), Veterans Affairs Medical Center, 4150 Clement St, San Francisco, CA 94121

Report of a Case

This 21-year-old woman was transferred to the medical facility at the University of California, San Francisco (UCSF) for continued treatment of Graves' disease and hepatic failure. She had been in good health until seven months before admission when she developed heat intolerance, tremor, weight loss, and palpitations. A clinical diagnosis of hyperthyroidism was confirmed by the findings of a free thyroxine (FT_4) level higher than 7 (normal range 0.9–2.1 ng/dL) and a thyroid-stimulating hormone (TSH) level lower than 0.1 (normal range 0.8–5 mU/L). Total bilirubin was normal at baseline, whereas aspartate aminotransferase (AST) and ALP levels were slightly elevated (Table 1). A course of PTU at 300 mg per day together with propranolol was initiated, after which the patient improved clinically while her FT_4 level decreased. Four and one-half months later, however, she presented with jaundice, abdominal pain, and signs of acute hepatitis (Table 1). Serology testing for hepatitis A and B viruses was negative. PTU and oral contraceptives were discontinued, and the patient's hyperthyroidism subsequently worsened. A radioactive iodine (RAI) uptake examination of the patient's thyroid gland revealed 75% uptake at 5 hours and 68% at 24 hours, and she was treated with RAI (28.3 mCi of ^{131}I) for thyroid ablation.

Three weeks after RAI treatment, the patient was readmitted to the hospital with fever and tachycardia. Her FT_4 level was higher than 7.5 ng/dl and her liver function had deteriorated. A workup for infection yielded negative results, and propranolol was replaced with atenolol. She was transferred to UCSF for further treatment.

The patient had no significant past medical illnesses except for a cholecystectomy performed two years previously. She had no history of liver disease, alcohol use, transfusion, drug abuse, or exposure to hepatitis, and no family history of liver disease. Her medications at the time of transfer included atenolol and cefotaxime. On physical examination, the patient was thin and markedly icteric but awake and oriented. Her blood pressure was 136/70 mm of mercury and her pulse rate was regular at 110 beats per minute. She was afebrile. Eye examination revealed slight proptosis with no lid lag or stare. The patient's thyroid gland was diffusely enlarged (approximate weight 50 g), mildly firm, and tender. A thyroid bruit was present and breath sounds were decreased at both lung bases. Cardiac examination showed a hyperdynamic precordium with tachycardia. Her liver and spleen were not palpable. Her liver span was 9 cm, and mild right upper quadrant tenderness and ascites were present. Pitting edema of both legs was noted. There was no asterixis.

Laboratory investigations showed a hemoglobin count of 8.8 mg%, a leukocyte count of 5,200 per mm^3,